NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF THEOPHYLLINE

(CAS NO. 58-55-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED AND GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

August 1998

NTP TR 473

NIH Publication No. 98-3963

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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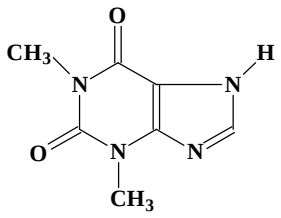
ABSTRACT



THEOPHYLLINE

CAS No. 58-55-9

Chemical Formula: $C_7H_8N_4O_2$ Molecular Weight: 180.17

Synonyms: 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione; 1,3-dimethylxanthine; 1H-purine-2,6-dione; NSC 2066; pseudotheophylline; theocin; theophylline, anhydrous

Trade names: Accurbron; Aerobin; Aerolate III; Afonilum; Aminophylline; Aquaphyllin; Armophylline; Asmalix; Bilordyl; Bronchoretard; Bronkodyl; Cetraphylline; Constant-T; Diffumal; Duraphyl; Duraphyllin; Elixicon; Elixophyllin; Euphylline L.A.; Euphylong; LaBID; Labophylline; Lanophyllin; Lasma; Liquophylline; Optiphyllin; Parkophyllin; Phylocontin; Physpan; Pro-Vent; PulmiDur; Pulmo-Timelets; Quibron; Respbid; Rona-Phyllin; Sabidal; Slo-bid; Slo-Phyllin; Solosin; Sustaire; Tefamin; Teobid; Teofyllamin; Tesona; Theal tablets; Theo-24; Theobid; Theocap; Theochron; Theoclear; Theocontin; Theo-Dur; Theofol; Theograd; Theolair; Theolan; Theolix; Theophyl; Theoplus; Theo-Sav; Theosol; Theospan; Theostat; Theovent; TheoX; T-Phyl; Truphylline; Uni-Dur; Unifyl; Uniphyl; Uniphyllin; Xanthium

Theophylline is an alkaloid found in tea (*Thea sinensis*) and chocolate and is structurally related to caffeine and theobromine. Theophylline is used as a pharmaceutical agent. It stimulates the heart and central nervous system, relaxes the smooth muscles of the bronchi and blood vessels, and causes diuresis. The drug is used mainly as a bronchodilator in obstructive airway diseases, such as bronchial asthma, and for myocardial stimulation. Theophylline was nominated for toxicologic and carcinogenicity testing as a representative of the purine structural subclass, particularly because of its relationship to purines such as caffeine, 1-methyl-3-hydroxyguanine, and 3-hydroxy-1-methylxanthine, the latter two compounds having been shown to induce sarcomas in rats. Additional reasons for testing theophylline included its widespread use in humans as a pharmaceutical agent, its possible genotoxicity *in vitro*, and the lack of information on its potential toxicity and/or carcinogenicity under conditions of chronic oral usage. Based on reported teratogenicity and testicular toxicity, it was also recommended that reproductive studies be included in the evaluation of theophylline. The oral route of administration was selected because it is the primary route of human exposure, and the gavage route was selected because it mimics the pharmaceutical use of theophylline in humans. Male and female F344/N rats and $B6C3F_1$ mice were given theophylline (greater than 99% pure) in feed or in corn oil by gavage for 16 days or 14 weeks or in corn oil by gavage for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, mouse bone marrow, and mouse peripheral blood.

16-DAY FEED STUDY IN RATS

Groups of five male and five female F344/N rats were given 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm theophylline in feed for 16 days, which resulted in approximate daily doses of 50, 100, 250, 450, or 1,000 mg theophylline/kg body weight to males and 75, 150, 250, 450, or 1,100 mg/kg to females. All rats

survived until the end of the study. The final mean body weights and body weight gains of 8,000 ppm males and females were significantly less than those of the controls. The absolute and relative testis weights of 4,000 ppm males were significantly greater than those of the controls. Increased incidences of uterine hypoplasia were observed microscopically in exposed groups of females.

16-DAY GAVAGE STUDY IN RATS

Groups of five male and five female F344/N rats were given 0, 12.5 (twice daily), 25 (once daily), 50 (once daily), 50 (twice daily), 100 (once daily), 200 (once daily), 200 (twice daily), or 400 (once daily) mg theophylline/kg body weight in corn oil by gavage. All rats receiving 400 mg/kg once daily and all but one female receiving 200 mg/kg twice daily died during the study. In groups dosed once daily, final mean body weights and body weight gains of males receiving 100 or 200 mg/kg and mean body weight gains of females receiving 50, 100, or 200 mg/kg were less than those of controls. The final mean body weights and body weight gains of groups receiving theophylline twice daily were generally similar to those of groups receiving the same daily dosages once daily. Clinical findings included rapid or labored respiration, hunched posture, and squinting. In groups dosed once daily, absolute and relative uterus weights of females receiving 100 or 200 mg/kg once daily were significantly less than those of the controls, and the absolute and relative uterus weights of females receiving 100 mg/kg once daily were significantly less than those of females receiving 50 mg/kg twice daily. Uterine atrophy was observed in three females receiving 200 mg/kg twice daily. Periarteritis of the mesenteric arteries was observed in two males and two females receiving 400 mg/kg once daily.

16-DAY FEED STUDY IN MICE

Groups of five male and five female $B6C3F_1$ mice were given 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm theophylline in feed for 16 days, resulting in approximate daily doses of 250, 475, 950, 1,800, or 2,000 mg theophylline/kg body weight to males and 300, 450, 1,225, 2,000, or 4,375 mg/kg to females. All mice survived until the end of the study. Final mean body weights of 4,000 and 8,000 ppm females and mean body weight gains of 2,000, 4,000, and 8,000 ppm females were significantly greater than those of the controls. Feed consumption by exposed groups was similar to that by the controls, except that by the 8,000 ppm males, which was approximately 40% the amount of feed consumed by the control group. Histopathologic examinations were not performed due to the absence of mortality and significant exposure-related lesions.

16-DAY GAVAGE STUDY IN MICE

Groups of five male and five female $B6C3F_1$ mice were given 0, 12.5 (twice daily), 25 (once daily), 50 (once daily), 50 (twice daily), 100 (once daily), 200 (once daily), 200 (twice daily), or 400 (once daily) mg theophylline/kg body weight in corn oil by gavage. Three males and all females receiving 400 mg/kg once daily died on day 1. There were no significant differences in final mean body weights or body weight gains. There were no histopathologic findings attributed directly to theophylline.

14-WEEK FEED STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were given 0, 1,000, 2,000, or 4,000 ppm theophylline in feed for 14 weeks, which resulted in approximate daily doses of 75, 125, or 250 mg theophylline/kg body weight to males and 75, 125, or 275 mg/kg to females. The final mean body weight of 1,000 ppm females was significantly greater than that of the control group. Feed consumption by exposed groups was similar to that by the controls. Mean cell volume and mean cell hemoglobin were significantly greater in males exposed to 2,000 or 4,000 ppm than those in the control group. Segmented neutrophil counts of all groups of exposed females were significantly greater than that of the control group. The absolute and relative kidney weights of 4,000 ppm males were significantly greater than those of the controls, and there was an exposure-related increase in the severity of nephropathy in males. Exposure-related increases in the incidences of mesenteric and/or pancreatic periarteritis were observed in males and females.

14-WEEK GAVAGE STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were given 0, 37.5, 75, or 150 mg theophylline/kg body weight in corn oil by gavage for 14 weeks. One male and one female receiving 150 mg/kg died before the end of the study. The mean body weight gain of 150 mg/kg females was significantly greater than that of the controls. Mean cell volume of 150 mg/kg males and mean cell hemoglobin of all groups of dosed males were significantly greater than those of the control group. There were slight dose-dependent increases in the incidences of mesenteric periarteritis in dosed males and females.

14-WEEK FEED STUDY IN MICE

Groups of 10 male and 10 female $B6C3F_1$ mice were given 0, 1,000, 2,000, or 4,000 ppm theophylline in feed for 14 weeks, resulting in approximate daily doses of 175, 400, or 800 mg theophylline/kg body weight to males and 225, 425, or 850 mg/kg to females. All mice survived until the end of the study. The final mean body weights and body weight gains of all exposed groups of males and females were significantly less than those of the controls. Feed consumption by exposed groups was similar to that by the controls. Leukocyte, segmented neutrophil, and lymphocyte counts of 4,000 ppm males were significantly greater than those of the controls. Leukocyte and segmented neutrophil counts of 2,000 or 4,000 ppm females were significantly greater than those of the controls. There were no histopathologic findings attributed directly to theophylline exposure.

14-WEEK GAVAGE STUDY IN MICE

Groups of 10 male and 10 female $B6C3F_1$ mice were given 0, 75, 150, or 300 mg theophylline/kg body weight in corn oil by gavage for 14 weeks. Three males and all females receiving 300 mg/kg, one 75 mg/kg male, and one control female died before the end of the study. Final mean body weights and body weight gains of 150 and 300 mg/kg males were significantly less than those of the controls. Mean cell volume and mean cell hemoglobin of 300 mg/kg males were significantly greater than those of the controls. There were no histopathologic findings attributed directly to theophylline treatment.

2-YEAR GAVAGE STUDY IN RATS

Groups of 50 male and 50 female rats were given 7.5, 25, or 75 mg theophylline/kg body weight in corn oil by gavage for 2 years.

Survival and Body Weights

There were no significant differences in survival between dosed and control groups. Final mean body weights of all groups of dosed males and females were significantly less than those of the controls.

Pathology Findings

There were no significantly increased incidences of neoplasms in dosed rats. The incidence of chronic inflammation of the mesenteric arteries was significantly increased in males receiving 75 mg/kg compared to the controls. There were dose-related negative trends in the incidences of mammary gland fibroadenoma and fibroadenoma or carcinoma (combined) in females; these differences correlated with decreased body weights.

2-YEAR GAVAGE STUDY IN MICE

Groups of 50 male $B6C3F_1$ mice were given 0, 15, 50, or 150 mg theophylline/kg body weight and groups of 50 female $B6C3F_1$ mice were given 0, 7.5, 25, or 75 mg/kg in corn oil by gavage for 2 years.

Survival and Body Weights

Survival of 150 mg/kg males was significantly less than that of the controls. The final mean body weights of 150 mg/kg males, 25 mg/kg females, and 75 mg/kg females were significantly less than those of the control groups.

Pathology Findings

There were no treatment-related increases in incidences of nonneoplastic lesions or neoplasms. In males and females, there were decreased incidences of hepatocellular adenoma and of the combined incidences of hepatocellular adenoma or carcinoma compared to the controls. Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms in the liver consistent with *Helicobacter hepaticus* infection. The incidences of these liver lesions in 150 mg/kg males were significantly lower than those in control males. Increases in the incidences of hepatocellular neoplasms in male

mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present. Because of this association, interpretation of the decreased incidence of liver neoplasms in male mice was more difficult. Incidences of lesions at other sites in this study were not considered to have been significantly impacted by *H. hepaticus* infection or its associated hepatitis.

GENETIC TOXICOLOGY

Theophylline was not mutagenic in *Salmonella typhimurium*, with or without metabolic activation (S9). It induced sister chromatid exchanges but not chromosomal aberrations in cultured Chinese hamster ovary cells. The positive sister chromatid exchange response was noted only in the absence of S9. *In vivo*, a mouse bone marrow sister chromatid exchange test showed positive results at a standard 23-hour harvest time; however, this test was not repeated and the response is unconfirmed. An *in vivo* mouse bone marrow chromosomal aberrations test, that employed both standard and extended exposure protocols, gave negative results. The frequency of micronucleated erythrocytes was determined in peripheral blood of male and female mice exposed to theophylline in dosed feed or in corn oil by gavage for 14 weeks. No significant increases in the frequencies of micronucleated cells were seen in male or female mice in either of the studies.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of theophylline in male or female F344/N rats administered 7.5, 25, or 75 mg/kg. There was *no evidence of carcinogenic activity* of theophylline in male B6C3F_1 mice administered 15, 50, or 150 mg/kg or female B6C3F_1 mice administered 7.5, 25, or 75 mg/kg.

Gavage administration of theophylline caused chronic inflammation of the mesenteric arteries in dosed male rats.

Decreased incidences of mammary neoplasms in female rats were likely associated with lower body weights. There were dose-related decreases in the incidences of hepatocellular adenoma and hepatocellular carcinoma in male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Theophylline

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 7.5, 25, or 75 mg/kg in corn oil by gavage	0, 7.5, 25, or 75 mg/kg in corn oil by gavage	0, 15, 50, or 150 mg/kg in corn oil by gavage	0, 7.5, 25, or 75 mg/kg in corn oil by gavage
Body weights	Dosed groups less than control group	Dosed groups less than control group	150 mg/kg group less control group	25 and 75 mg/kg groups less than control group
2-Year survival rates	23/50, 33/50, 29/50, 24/50	32/50, 30/50, 33/50, 33/50	36/50, 35/50, 44/50, 26/50	37/50, 37/50, 34/50, 33/50
Nonneoplastic effects	Mesenteric artery: chronic inflammation (2/50, 2/50, 3/50, 15/50)	None	None	None
Neoplastic effects	None	None	None	None
Decreased incidences	None	Mammary gland: fibroadenoma (22/50, 19/50, 12/50, 12/50); fibroadenoma or carcinoma (23/50, 20/50, 12/50, 12/50)	Liver: hepatocellular adenoma (21/50, 18/50, 12/50, 2/50); hepatocellular carcinoma (19/50, 14/50, 12/50, 2/50); hepatocellular adenoma or carcinoma (34/50, 27/50, 22/50, 4/50)	Liver: hepatocellular adenoma (20/50, 11/50, 12/50, 3/50); hepatocellular carcinoma (11/50, 5/50, 6/50, 5/50); hepatocellular adenoma or carcinoma (29/50, 14/50, 18/50, 8/50)
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Positive without S9
Mouse bone marrow *in vivo*:	Positive
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with or without S9
Mouse bone marrow *in vivo*:	Negative
Micronucleated erythrocytes	
Mouse peripheral blood *in vivo* (feed study):	Negative
Mouse peripheral blood *in vivo* (gavage study):	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on theophylline on 11 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996 the draft Technical Report on the toxicology and carcinogenicity studies of theophylline received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. P.C. Chan, NIEHS, introduced the toxicology and carcinogenesis studies of theophylline by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in male rats. The proposed conclusions for the 2-year studies in rats and mice were *no evidence of carcinogenic activity* in male or female F344/N rats or B6C3F$_1$ mice.

Dr. Reddy, a principal reviewer, agreed with the proposed conclusions. He said it would be useful to include information on the theophylline concentration per cup of tea and average daily consumption in tea drinkers. Dr. Chan said that it was a very small amount but wide ranging due to different kinds of tea and preparations. Dr. Reddy asked why the decision was made not to do histopathologic examination of tissues from mice fed theophylline for 16 days. Dr. Chan said that these animals were used only for dose selection and there was no mortality. Dr. Reddy wondered whether the periarteritis was due to the drug or to the *Helicobacter* infection. Dr. J.R. Hailey, NIEHS, observed that *Helicobacter* is not reported to have effects on vasculature outside of the liver.

Dr. Taylor, the second principal reviewer, agreed with the proposed conclusions. He thought a more extensive discussion of the periarteritis should be included, noting that in human medicine this can represent a fairly serious and life-threatening condition, which can occur after the administration of certain drugs. Dr. A. Nyska, NIEHS, commented that this lesion is characteristic of vasodilator drugs and was observed only in rats and only in the mesenteric arteries.

Dr. W.T. Allaben, NCTR/FDA, recommended that comments be made in the conclusions regarding the decreases in liver cancer in treated mice and mammary gland cancer in rats. Dr. J.R. Bucher, NIEHS, said this would be done. Dr. Goldsworthy said there also should be comment on significant decreases in body weight gain in the conclusions.

Dr. Reddy moved that the Technical Report on theophylline be accepted with the revisions discussed and the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Taylor seconded the motion, which was accepted unanimously with nine votes.